REMARKS

Claims 1-5, 7-11, and 16-20 are pending in the present application.

At the outset, Applicants wish to thank Examiner Carter and Examiner Padmanabhan for the helpful and courteous discussion with their undersigned Representative on March 5, 2008. During this discussion, several amendments and arguments were discussed to address the rejections of record. The content of this discussion is reflected in the amendments and remarks set forth herein. Reconsideration of the outstanding rejections is requested.

The rejections of: (a) Claims 1-5, 12, and 13 under 35 U.S.C. §103(a) over Nakajima et al in view of Georges et al, and (b) Claims 6, 7, 14, and 15 under 35 U.S.C. §103(a) over Nakajima et al in view of Georges et al and Ueda et al, are respectfully traversed.

The Examiner has taken the position that the claims are obvious over Nakajima et al (Exp. Cell Res. 1998) in view of Georges et al, with or without Ueda et al (J. of Antibotics, 1994). It is the Examiner's position that Nakajima et al disclose that FK228 is an inhibitor of intracellular histone deacetylase activity which strongly inhibits proliferation of tumor cells *in vitro* and greatly suppresses the growth of transplanted tumors in mice. However, the Examiner recognizes that Nakajima et al fail to specifically disclose the treatment of kidney cancer or suppression of a cancerous tumor in the kidney.

In an attempt to compensate for this deficiency, the Examiner cites Georges et al. Georges et al discloses that an unrelated collection of compounds have been found to possess anti-cell-proliferation properties arising from their histone deacetylase inhibitory activity (see paragraph [0036]). Georges et al then concludes that due to the anti-cell-proliferation

properties, their compounds "are expected to be useful in the treatment of cancer... particularly in the treatment of cancers of the breast, lung, colon, rectum, stomach, prostate, bladder, pancreas, and ovary." Georges et al further speculate that "It is in addition expected that a derivative of the present invention will possess activity against a range of leukemias, lymphoid malignancies and solid tumors such as carcinomas and sarcomas in tissues such as the liver, kidney, prostate and pancreas" (see paragraph [0036]).

Using the HDAC inhibitory activity, the Examiner concludes that the treatment of cancer and/or suppression of cancerous tumors in the kidney would have been obvious to the skilled artisan. Applicants submit that the combined disclosures of Nakajima et al and Georges et al, with or without Ueda et al, fail to provide a reasonable expectation of success.

Specifically, from the cited sections above, Georges et al disclose that their compounds are "expected" to be useful in the treatment of a vast array of etiologically distinct cancers. No reasonable nexus or evidence is provided by Georges et al or the Examiner to show that the artisan would have a reasonable basis to expect that any HDAC inhibitor, including those disclosed in Georges et al as well as FK228, would be effective for treating any form of cancer from those recited. Thus, the statement in Georges et al can amount to nothing more that a wish or a hope, which at best offers an invitation to experiment. However, "obvious to try" has long been held *not* to constitute obviousness. *In re O'Farrell*, 7 USPQ2d 1673, 1680-81 (Fed. Cir. 1988). A general incentive (i.e., "a desire to enhance the production of 2'-deoxyribonucleosides") does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out. *In re Deuel*, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995).

In the Office Action mailed November 30, 2007, the Examiner makes the following allegation with respect to "expectation of success":

> Particularly, the use of the HDAC inhibitors of Georges et al. expected use for the treatment of kidney cancers (see page 3, paragraph 36) is enough for a skilled practitioner to obviously try other HDAC inhibitors. The expectation of success is that a mechanism of action has been established between HDAC inhibitors and several cancers. Thus, although the structures of inhibitors may be different, the compounds have the same mechanism of action.

Applicants disagree.

On page 3, paragraph 36, Georges et al indicate that their compounds "are expected to be useful in the treatment of cancer", and recite most of the organs as tumor sites where the effect of a caner treatment is expected. Therefore, it is clear that the effectiveness was not actually confirmed, but rather speculated. In fact, Georges et al merely disclose that the compound has an HDAC inhibitory activity (page 10, Example 12) and do not provide any data supporting the usefulness of the compound for cancer in each organ, especially the kidney.

In contract, as shown on page 556, Table 4, of Nishimura et al, The Journal of Antibiotics Vol. XLII No. 4 (April 1989): 553-557 (**submitted herewith**), the skilled artisan usually performs an *in vivo* cancer growth inhibition test (sensitivity test) for a target cancer in order to determine the site and the kind of cancer for which an anticancer drug is effective. Moreover, as shown in Table 4 concerning FR900840 described in Nishimura et al, it is known that each anticancer drug shows different effects depending on the tumor site and the kind of cancer cells. Thus, from the disclosure of Georges et al, it is difficult for the artisan to determine whether or not the compound disclosed therein is indeed effective for kidney cancer. It is even more difficult to consider that Georges et al provide a motivation to expect a specific effect for kidney cancer of other HDAC inhibitors having different structures.

Applicants strongly argue that it is not proper to conclude, "use for the treatment of kidney cancers is enough for a skilled practitioner to obviously try" with regard to the compound of the present invention. The reasons therefore are that Georges et al the Examiner relies on only provide a broad disclosure with a desirous effect of the compound but without a support for the alleged effect, the present compound has a completely different structure, and that the mere presence of the same mechanism is not sufficient to reach such conclusion.

Further, Applicants again wish to direct the Examiner's attention to page 2, lines 2-7, which provides a general view of the state of the art at the time of the present invention stating:

> As the situation stands, however, there are many problems yet to be solved, such as effectiveness of *in vitro* results in *in vivo* application, *in vivo* effectiveness against any tumor and the like. The antitumor activity *in vitro* against kidney cancer has been reported, but an antitumor activity *in vivo* against kidney cancer has not been reported.

Based on the foregoing, Applicants submit that there is no direct expectation of *in vivo* efficacy from the *in vitro* observation of HDAC inhibitory activity. This lack of expectation of success is clearly manifest in the combined disclosures of Nakajima et al and Georges et al. Nonetheless, the Examiner states on page 11 of the Office Action, "In regards to expectation of success for *in vivo* efficacy based on *in vivo* data, the prior art demonstrates that *in vitro* data does relate to efficacy of kidney tumors *in vivo*, as taught by Ueda et al." The Examiner's opinion seems to involve a misunderstanding, as described below.

The Examiner's apparent position is that the experiment bridging pages 303-304. However, Applicants respectfully submit that the cell lines used in this *in vivo* study are A549 and MCF-7, which are human ***lung*** adenocarcinoma and human ***mammary*** adenocarcinoma respectively. Further, the above-referenced text clearly states that these cells were transplanted ***under*** the kidney capsule of BDF1 mice. Thus, none of these experiments provide any

suggestion to ***treat kidney cancer*** or any expectation of the efficacy when so doing. Therefore, Ueda et al does nothing to compensate for the deficiency in the combined disclosures of Nakajima et al and Georges et al.

With regard to the disclosure of Ueda et al, the Examiner states on page 12 of the Office Action mailed November 30, 2007:

> The Examiner disagrees because the origin of the cell line (i.e. lung or mammary) are irrelevant in this case because the tumors are implanted under the kidney capsule and then the tumor size is measured. Thus, the kidney now has the tumor and not the lung or breast."

Applicants submit that this allegation is without merit. The Examiner is reminded that lung cancer cell lines, breast cancer cell lines, and kidney cancer cell lines are distinct. As such, just because a breast cancer cell is grown *on* the kidney does not instantly make it "kidney cancer." It remains a breast cancer cell that is grown on the kidney.

Further, the following is found in Ueda et al on page 303, lines 6-4 from the bottom, which clarifies that the *in vivo* test uses the method of Nishimura et al called SRC assay:

> "In Vivo Antitumor Activity of FR901228
> A two-week Subrenal Capsule (SRC) assay using the immunosuppressive agent FK-506 was performed according to the method described by Nishimura et al.[17,18]"

In response, Applicants **submit herewith** the following references:

Nishimura et al, The Journal of Antibiotics Vol. XLII No. 4 (April 1989): 553-557;

Abstract of Gan to Kagaku Ryoho, 1987 May; 14 (5 Pt 2): 1629-35; and

Bogden et al, Exp Cell Biol. 1979; 47(4): 281-93.

In Nishimura et al., the Subrenal Capsule (SRC) Assay is described on page 555. In addition, Gan to Kagaku Ryoho, 1987 May; 14 (5 Pt 2): 1629-35 and Exp Cell Biol. 1979; 47(4): 281-93 discuss the SRC Assay. These references teach that the SRC Assay is a sensitivity test

(chemosensitivity test) of anticancer drugs and, by comparison with a subcutaneous transplantation assay in nude mice, they state that the tumor growth inhibition rates of the SRC assay were corrected well with the clinical responses.

Therefore, it will be understood that the SRC Assay is a sensitivity test for rapid evaluation of a clinical affect of an anticancer drug for various tumors. While a tumor is implanted under the kidney capsule in the test of Ueda et al, this is clearly not for the evaluation of the effect on kidney cancer, but for the evaluation of the clinical effect of the compound on the implanted tumor itself (i.e. lung or mammary).

Therefore, the Examiner's position mentioned earlier, "the prior art demonstrates that in vitro data does relates to efficacy of kidney tumors in vivo, as taught by Ueda et al." stems from an incorrect understanding of the SRC Assay, and it is clear that Ueda et al do not at all suggest the efficacy for kidney tumors *in vivo*.

With respect to Bogden et al, the Examiner is referred to the Discussion on page 290, which discloses that an environment promoting the growth of xenografts (namely, human cancer cells) is present in the subrenal capsule site (first paragraph), and that the xenograft itself can be visualized due to the transparency of the renal capsule (third paragraph). It is therefore obvious that the SRC technique is a useful test method for measuring the growth of the implanted human cancer cells, utilizing the environment of the subrenal capsule site. In addition, the fourth paragraph on page 291 discloses that this method enables screening of drugs against a wider range of human tumor systems, and also enables evaluation of organ specificity as well as clinical potential. In contrast, no disclosure is found which indicates or suggests formation of kidney cancer in the subrenal capsule by the human cancer cell implanted by this method, as alleged by the Examiner.

Further, in the Results on page 284 of Bogden et al, the growth of human cancer cells implanted under the renal capsule is disclosed in Figs. 1-6, where the results obtained by this test method concern growth of the implanted human cancer cells. Nishimura et al, The Journal of Antibiotics Vol. XLII No. 4 (April 1989): 553-557, describe in Activity against Human Xenograft Tumors on page 556 that the anticancer activity of FR900840 against 10 kinds of human cancers was evaluated by this test. Therefore, those skilled in the art understand that the SRC technique is a test method for evaluating anticancer activities of a drug against implanted human cancer cells, and even if the site of cell implantation is under the renal capsule, they obviously do not consider that the technique evaluates action on kidney cancer.

Furthermore, Nishimura et al, The Journal of Antibiotics Vol. XLII No. 4 (April 1989): 553-557 disclose on page 556, Table 4 and in lines 10 to 3 from the bottom that an *in vivo* test was performed using the FR900840 compound against 10 different tumors and the results deny activity of the compound in certain kinds of tumors. This suggests that the activity of a compound against a tumor cannot be predicted based only on an *in vivo* activity of the compound against a different kind of tumor. Therefore, contrary to the Examiner's allegation, the skilled artisan would *not* reasonably expect that the present compound would treat a tumor in the kidney in vivo based on the disclosure of Ueda et al.

It is further submitted that the presently claimed invention is drawn to an *in vivo* method. The Examiner recognizes that "Nakajima et al. and Georges et al. do not teach the Applicant's compound used *in vivo* or in a human". Thus, for the reasons given above, the presently claimed invention is not obvious from the combined disclosures of Nakajima et al and Georges et al.

With respect to the Examiner's additional statement on page 12 of the Office Action mailed November 30, 2007, "This test is similar to that done by the Applicant in which human renal tumor cells are implanted into the right flank of BALB mice to test in vivo efficacy (see specification, page 13, section (3), (4) and (6)." Applicants submit that, as stated above, the test performed in the present invention was not an SRC Assay but an ordinary subcutaneous implantation assay for evaluation of *in vivo* renal tumor growth inhibitory activity. Therefore, this test clearly indicates that the compound of the present invention suppresses growth of a cancerous tumor of the kidney *in vivo*. None of the cited art makes the claimed invention obvious.

In view of the foregoing, Applicants request withdrawal of these grounds of rejection.

Finally, the Examiner has issued the following obviousness-type double patenting rejections:

(a) Claims 1-7 and 12-15 over Claims 1-3 and 9 of co-pending application No. 11/064,292;

(b) Claims 1-7 and 12-15 over Claims 60-62, 69, and 70 of co-pending application No. 10/948,288 (now US 7,314,862); and

(c) Claims 1-7 and 12-15 over Claims 45 and 60 of co-pending application No. 10/486,833 in view of Georges et al.

On page 2 of the Office Action mailed November 30, 2007, the Examiner provided the following statement "the Examiner acknowledges Applicant's indication that a terminal disclaimer will be filed upon identification of allowable subject matter to obviate to the provisional obviousness-type double patenting rejections over U.S. Patent Application No.

11/064,292, 10/948,288, and 10/486,833."

However, there are a couple problems with this statement by the Examiner. First, Applicants did *not* indicate that a terminal disclaimer will be filed upon identification of allowable subject matter to obviate to the provisional obviousness-type double patenting rejections. On the contrary, Applicants provided the following statement:

> Finally, Applicants respectfully request that the provisional obviousness-type double patenting rejections of: (a) Claims 1-7 and 12-15 over Claims 1-3 and 9 of co-pending application No. 11/064,292; (b) Claims 1-7 and 12-15 over Claims 60-62, 69, and 70 of co-pending application No. 10/948,288; and (c) Claims 1-7 and 12-15 over Claims 45 and 60 of co-pending application No. 10/486,833 in view of Georges et al, be held in abeyance until an indication of allowable subject matter in the present application. *If necessary, a terminal disclaimer will be filed at that time.* Until such a time, Applicants make no statement with respect to the propriety of this ground of rejection.

In the foregoing statement, Applicants stated that a terminal disclaimer would be filed "if necessary." This leads to the second problem with the Examiner's statement – the claims of the cited co-pending applications do not render the claimed invention obvious.

For example, the claims of US 11/064,292 do not specifically relate to the suppression of a cancerous tumor in the kidney. Thus, for the same reasons presented above, in view of this deficiency the claimed invention is not obvious in view of US 11/064,292. Further, Claims 45 and 60 of US 10/486,833 relate to a method of treating prostate cancer, not kidney cancer. There is nothing in these claims or in Georges et al to render the present invention obvious. The claims of US 10/948,288 (now US 7,314,862) require a synergistic formulation of a histone deacetylase inhibitor and doxorubicin. None of the claims of this application remotely suggest the effect on kidney cancer of the compound of formulae (1) or (2) in the absence of doxorubicin. Thus, the present invention is not obvious.

Finally, the Examiner is reminded that MPEP §804 indicates that: "If "provisional" ODP rejections in two applications are the only rejections remaining in those applications, the examiner should withdraw the ODP rejection in the earlier filed application thereby permitting that application to issue without need of a terminal disclaimer." Of the three applications that are still pending (the present application, US 11/064,292, and US 10/486,833), the present application has the earliest effective filing date[1] (i.e., is the earlier filed application) and, therefore, if this application is in condition for allowance the obviousness-type double patenting rejections over US 11/064,292, and US 10/486,833 should be withdrawn.

In view of the foregoing, Applicants request withdrawal of these grounds of rejection.

Applicants submit that the present application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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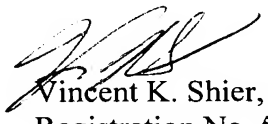
Norman F. Oblon



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[1] The present application has an effective filing date of US 60/369,868 of April 5, 2002, while the effective filing date of US 11/064,292, and US 10/486,833 is April 29, 2004 and August 20, 2002, respectively.